Menthol Alone Upregulates Midbrain nAChRs, Alters nAChR Subtype Stoichiometry, Alters Dopamine Neuron Firing Frequency, and Prevents Nicotine Reward.

Journal: J Neurosci

Publication Year: 2016

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PubMed link: 26961950

Funding Grants: Bridges to Stem Cell Research at Pasadena City College

Public Summary:
Upregulation of beta2 subunit-containing (beta2*) nicotinic acetylcholine receptors (nAChRs) is implicated in several aspects of nicotine addiction, and menthol cigarette smokers tend to upregulate beta2* nAChRs more than nonmenthol cigarette smokers. We investigated the effect of long-term menthol alone on midbrain neurons containing nAChRs. In midbrain dopaminergic (DA) neurons from mice containing fluorescent nAChR subunits, menthol alone increased the number of alpha4 and alpha6 nAChR subunits, but this upregulation did not occur in midbrain GABAergic neurons. Thus, chronic menthol produces a cell-type-selective upregulation of alpha4* nAChRs, complementing that of chronic nicotine alone, which upregulates alpha4 subunit-containing (alpha4*) nAChRs in GABAergic but not DA neurons. In mouse brain slices and cultured midbrain neurons, menthol reduced DA neuron firing frequency and altered DA neuron excitability following nAChR activation. Furthermore, menthol exposure before nicotine abolished nicotine reward-related behavior in mice. In neuroblastoma cells transfected with fluorescent nAChR subunits, exposure to 500 nm menthol alone also increased nAChR number and favored the formation of (alpha4)3(beta2)2 nAChRs; this contrasts with the action of nicotine itself, which favors (alpha4)2(beta2)3 nAChRs. Menthol alone also increases the number of alpha6beta2 receptors that exclude the beta3 subunit. Thus, menthol stabilizes lower-sensitivity alpha4* and alpha6 subunit-containing nAChRs, possibly by acting as a chemical chaperone. The abolition of nicotine reward-related behavior may be mediated through menthol's ability to stabilize lower-sensitivity nAChRs and alter DA neuron excitability. We conclude that menthol is more than a tobacco flavorant: administered alone chronically, it alters midbrain DA neurons of the nicotine reward-related pathway.

Scientific Abstract:
Upregulation of beta2 subunit-containing (beta2*) nicotinic acetylcholine receptors (nAChRs) is implicated in several aspects of nicotine addiction, and menthol cigarette smokers tend to upregulate beta2* nAChRs more than nonmenthol cigarette smokers. We investigated the effect of long-term menthol alone on midbrain neurons containing nAChRs. In midbrain dopaminergic (DA) neurons from mice containing fluorescent nAChR subunits, menthol alone increased the number of alpha4 and alpha6 nAChR subunits, but this upregulation did not occur in midbrain GABAergic neurons. Thus, chronic menthol produces a cell-type-selective upregulation of alpha4* nAChRs, complementing that of chronic nicotine alone, which upregulates alpha4 subunit-containing (alpha4*) nAChRs in GABAergic but not DA neurons. In mouse brain slices and cultured midbrain neurons, menthol reduced DA neuron firing frequency and altered DA neuron excitability following nAChR activation. Furthermore, menthol exposure before nicotine abolished nicotine reward-related behavior in mice. In neuroblastoma cells transfected with fluorescent nAChR subunits, exposure to 500 nm menthol alone also increased nAChR number and favored the formation of (alpha4)3(beta2)2 nAChRs; this contrasts with the action of nicotine itself, which favors (alpha4)2(beta2)3 nAChRs. Menthol alone also increases the number of alpha6beta2 receptors that exclude the beta3 subunit. Thus, menthol stabilizes lower-sensitivity alpha4* and alpha6 subunit-containing nAChRs, possibly by acting as a chemical chaperone. The abolition of nicotine reward-related behavior may be mediated through menthol's ability to stabilize lower-sensitivity nAChRs and alter DA neuron excitability. We conclude that menthol is more than a tobacco flavorant: administered alone chronically, it alters midbrain DA neurons of the nicotine reward-related pathway.